Dopaminergic Augmentation in Restless Legs Syndrome/Willis-Ekbom Disease: Identification and Management

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KEYWORDS

• Restless legs syndrome • Augmentation • Rebound • Management • Disease progression

KEY POINTS

- Augmentation is the main clinical complication of long-term dopaminergic treatment of restless legs syndrome (RLS)/Willis-Ekbom disease and also the main reason for treatment failure of this class of drugs.
- It involves an increase in the severity of RLS symptoms during treatment.
- The incidence of augmentation increases with higher doses of dopaminergics and with longer duration of treatment.
- There is preliminary evidence showing that the incidence of augmentation is higher when short-acting dopamine agonists are used.
- Prevention strategies include managing lifestyle changes and keeping dopaminergic load as low as possible by performing in previously untreated patients, whenever feasible, a treatment trial with nondopaminergic agents.
- Treatment of augmentation might require switching to longer-acting dopaminergic agents and, in severe cases, switching to alpha-2 delta ligands (if not already tried before) or opiates.

INTRODUCTION

Since the first introduction of dopaminergic agents in 1982,[1] the overall long-term efficacy of these drugs has been well established by several retrospective studies.[2–4] Side effects are generally mild and, contrary to the observations performed during treatment with L-3,4-dihydroxyphenylalanine (L-DOPA) in Parkinson disease, cases of dyskinesia have yet to be reported.[3]

Despite the widespread use of dopaminergic drugs for restless legs syndrome (RLS)/Willis-Ekbom disease (WED), it was not until 1996 that the first clinical description of augmentation as a complication of dopaminergic treatment was made. Allen and Earley[5] described a group of 30 patients with RLS/WED who had been treated with L-DOPA, and described a condition characterized by an earlier onset of symptoms in the afternoon along with a faster onset of symptoms when at rest, an expansion of symptoms to the upper limbs and the trunk, an overall increase in severity/frequency, and a shorter effect of the medication. Under L-DOPA, augmentation of RLS/WED symptoms occurred in 82% of the patients and was severe enough to require change of treatment in 50%.[5] The most characteristic feature of the new condition occurring during long-term treatment with L-DOPA was that there was an increase in severity beyond the one seen at baseline, a feature that differentiated it from rebound or from tolerance (ie, seen under benzodiazepines or in opiates). In other words, augmentation is a drug-induced increase in RLS/WED symptom severity beyond that experienced before

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treatment was initiated, and this remains the most characteristic feature of dopaminergic augmentation, compared with pharmacologic tolerance.

CLINICAL DEFINITION

It is difficult to examine the augmentation rates for different drugs given that for a long time there was no standardized operational definition of this condition. The need to standardize clinical diagnostic criteria for augmentation was first recognized by the National Institutes of Health (NIH) who sponsored a workshop on RLS Diagnosis and Epidemiology in 2002.[6] This consensus conference generated an operational definition of augmentation, the primary feature of which was defined as a drug-induced shifting of symptoms to a period of time 2 hours earlier than was the typical period of daily onset of symptoms before pharmacologic intervention. The 2003 definition was based exclusively on clinical experience rather than on empirical data. Neither included guidelines on how to assess the severity or clinical significance of augmentation. This task was tackled several years later, in 2006, by a European Restless Legs Syndrome Study Group–sponsored consensus conference at the Max-Planck Institute in Munich (Germany) during which, based on empirical data from clinical studies, a better operational definition for the clinical identification of augmentation was sought. These studies indicated that reliable detection of augmentation could be obtained based on a 4-hour time advance of symptoms, or a smaller (2–4 hours) advance of symptoms expressed along with other required clinical indications,[7] such as a shorter latency of symptoms at rest, a spread of symptoms to other body parts in addition to the lower limbs, or a greater intensity of symptoms. In addition, the paradoxic response to treatment, reflected by an increase in severity with increasing dose of medication, and an improvement following decreases in medication, was considered an alternative key feature for diagnosis (**Box 1**).

Several studies have been able to correlate the presence of augmentation during treatment with dopaminergic agents with the duration of treatment and with a higher medication dosage, but not with symptom severity at baseline, age or gender.[8–10] Clinical experience shows that, when

Box 1
Max-Planck-Institute criteria

Preamble

Augmentation is a worsening of RLS symptom severity experienced by patients undergoing treatment of RLS. The RLS symptoms in general are more severe than those experienced at baseline.

A. Basic features (all of which need to be met):
   1. The increase in symptom severity was experienced on 5 out of 7 days during the previous week.
   2. The increase in symptom severity is not accounted for by other factors, such as a change in medical status, lifestyle, or the natural progression of the disorder.
   3. It is assumed that there has been a prior positive response to treatment.

In addition, B, C, or both have to be met:

B. Persisting (although not immediate) paradoxic response to treatment: RLS symptom severity increases some time after a dose increase, and improves some time after a dose decrease.

C. Earlier onset of symptoms:
   1. An earlier onset by at least 4 hours.

      Or:

   2. An earlier onset (between 2 and 4 hours) occurs with one of the following compared with symptom status before treatment:
      a. Shorter latency to symptoms when at rest
      b. Spreading of symptoms to other body parts
      c. Intensity of symptoms is greater (or increase in periodic limb movements if measured by polysomnography or the suggested immobilization test)
      d. Duration of relief from treatment is shorter

Augmentation requires criteria A and B, A and C, or A and B and C to be met.